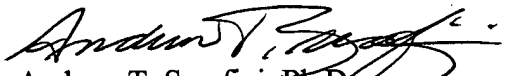
The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

In support of this amendment, Applicant states that this also corrects several minor typographical errors. These corrections would have been obvious to one skilled in the art. The first targeted molecule was well described in the application, and the fact that it had the sequence GGGVFWQ rather than GGGVFNQ (page 53, lines 7,9,11,24 and 29; page 55, line 21,22 and 26) or rather than GGGVPWQ (page 55, line 27) would have been readily apparent to a reader of ordinary skill.

Applicants believe that no fee is required for this submission. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-324-2400.

Respectfully submitted,



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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**IN THE SPECIFICATION:**

On page 1 at line 6 please add the following:

**--CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a divisional of, and claims the benefit of priority from, U.S. Patent Application Serial No. 09/327,045, filed June 7, 1999, now abandoned, the full disclosure of which is incorporated herein by reference in its entirety.--

Paragraph beginning at page 27, line 2, has been amended as follows:

Preferred targeting molecules of the invention comprise an amino acid sequence selected from the group comprising GGGVFWQ, HGRVRPH, VVLVTSS, CLHRGNSC, and CRSWNKADNRSC (SEQ ID NO:1-5, respectively) using the *in vivo* panning procedure described above and referenced below. The GGGVFWQ , HGRVRPH, VVLVTSS, and CLHRGNSC (SEQ ID NO:1-4, respectively) peptides selectively bind to normal cardiac endothelium. More specifically, the GGGVFWQ (SEQ ID NO:1) peptide showed a 5-fold enrichment to normal cardiac vasculature, while the HGRVRPH, VVLVTSS, CLHRGNSC (SEQ ID NO:2-4, respectively) peptides showed a 2-fold enrichment to normal cardiac vasculature. The CRSWNKADNRSC (SEQ ID NO:5) peptide showed 5-fold enrichment to ischemic myocardium. Details of how these peptides were identified and their properties are described in U.S.S.N. 09/326,718 [Campbell & Flores LLP Attorney Docket # P-LJ 3512] filed on even date herewith which is specifically incorporated herein by reference.

Paragraph beginning at page 48, line 25, has been amended as follows:

The plasmid pVEGF-Bwt167 is constructed by insertion of a 580bp PCR product derived from phage Lambda gt11-VEGF-Bwt167 into the expression plasmid pSI (Promega, Inc.). This phage is obtainable by screening a human fibrosarcoma cDNA library in lambda g11 (obtainable from Clontech, Inc.). The PCR reaction is performed employing the

Advantage KlenTaq Polymerase Mix system (Clontech. Inc.) in a final volume of 100 microliter containing lng of the plasmid template, 0.5μM of primers P-wt167(l) [5-GATCGCTAGC GGCAGCATGA GCCCTCTGCT CCGCCGCCTG-3'] 5'-GATCGCTAGC GGCAGCATGA GCCCTCTGCT CCGCCGCCTG-3' (SEQ ID NO:6) and P-wt167(2) 5'-TGACGCGGCC GCTCACCTTC GCAGCTTCCG GCACCTGCAG-3' (SEQ ID NO:7) as well as 0.2mM dNTPs, using the conditions 93°C 30 sec, 55°C 30 sec, 72°C 30 sec for 30 cycles followed by a 72°C 10 min extension in a Pharmacia LKB Gene ATAQ Controller PCR. system. The PCR product is gel-purified, digested with NheI and NotI and ligated into the NheI/NotI cleaved plasmid pSI. The resulting plasmid is designated pVEGF-Bwt167.

Paragraph beginning at page 49, line 8, has been amended as follows:

**EXAMPLE 2**

**Coupling of Peptide GGGVFWQ (SEQ ID NO:1) to VEGF-$B_{167}$**

Principle

The N-terminally blocked peptide is activated at the C-terminus by the water soluble carbodiimide EDC (N-Ethyl-N'(3-dimethylaminopropyl) carbodiimide in the presence of N-hydroxysuccinimide (NHS). The activated peptide then reacts with the primary amino groups of the VEGF molecule. By adjusting the pH carefully it is possible to direct this reaction towards the N-terminus of the VEGF-$B_{167}$ molecule (*see, e.g.*, Staros, J. *et al.*, *Anal. Biochem.* (1986) 156: 220-222 and Wong, S.S., "Application of Chemical Crosslinking to Soluble Proteins" in: CHEMISTRY OF PROTEIN CONJUGATION AND CROSSLINKING, (CRC Press Inc. 1993), pp. 221-229; these references and the references cited therein are incorporated herein by reference).

Paragraph beginning at page 50, line 5, has been amended as follows:

**EXAMPLE 3**

**Coupling of a C-terminal elongated peptide GGGVFWQ (SEQ ID NO:1) to VEGF-$B_{167}$**

Principle

To avoid sterical hindrance during the binding of VEGF-B chimeric molecule to the VEGF receptor resp. to the targeting peptide receptor the peptide can be elongated by several additional amino acids on the C-terminal end. The C-terminal spacer should allow maximal flexibility while not interfering in the binding mechanism of VEGF and/or peptide to their specific receptors. Usually poly-Gly or poly-Ala sequences fulfill these requirements.

Paragraph beginning at page 50, line 17, has been amended as follows:

**EXAMPLE 4**

**Coupling of peptide GGGVFWQ (SEQ ID NO:1) to VEGF-$B_{167}$ by using a heterobifunctional reagent with a spacer domain**

Principle

The coupling of the peptide can also be performed by reacting the N-terminus of the peptide with the amine-reactive part of a heterobifunctional crosslinker (for example SMBP), whereupon the activated peptide then reacts with an accessible sulfhydril group of VEGF-$B_{167}$ to form a thioether linkage (*see, e.g.*, Staros, J. *et al.*, *Methods Enzymol.* (1989) 172, 609 and Wong, S.S., "Application of Chemical Crosslinking to Soluble Proteins" in: CHEMISTRY OF PROTEIN CONJUGATION AND CROSSLINKING, (CRC Press Inc. 1993), pp. 221-229). In the case of using SMBP the length of the spacer is in the order of 1.5nm. It has to be kept in mind that the sulfhydril group involved in the coupling reaction is not essential for the binding to the receptor protein.

Paragraph beginning at page 51, line 9, has been amended as follows:

**EXAMPLE 5**

**Non-covalent coupling of peptide GGGVFWQ (SEQ ID NO:1) to VEGF-$B_{167}$**

Principle

Ionic interaction is one of the dominant forces in forming protein structures. By introducing regions of opposite charge into macromolecules it is possible to form tight complexes between two reaction partners which are also stable under physiological conditions. The introduction of these charged amino acids has to be compatible with the function of both molecules.

Paragraph beginning at page 51, line 17, has been amended as follows:

Method

The peptide GGGVFWQ (SEQ ID NO:1) has to be modified at the N- or C-terminus by a stretch of 4-6 charged amino acids (Lysine, Arginine for the introduction of positive charges, Glutamic or Aspartic acid for the introduction of negative charges). Also the VEGF-$B_{167}$ has to be extended preferably at the N-terminus with a sequence of 4-6 charged amino acids. Once the reaction partners are synthesized and purified to the appropriate degree of quality, the complexes can be formed easily just by mixing the equivalent amounts of the opposite charged reaction partners. Separation of unreacted molecules from conjugates can be performed using Ion Exchange Chromatography.

Paragraph beginning at page 52, line 1, has been amended as follows:

**EXAMPLE 6**

**Conjugation of VEGF-$B_{167}$ to a His-tagged peptide GGGVFWQ (SEQ ID NO:1)**

Principle

In the case a complete separation of the VEGF chimeric molecule from free VEGF-$B_{167}$ is necessary, the peptide can be elongated on the N- or C-terminal end with a stretch of 4-6 Histidine molecules. The coupling reaction is then performed according to example 2 or 5. For the capture of VEGF-B chimeric molecules, the approach of metal affinity chromatography can be used (Porath, J. *et al.*, *Nature* (1975) 258: 598-599).

Paragraph beginning at page 52, line 16, has been amended as follows:

**EXAMPLE 7**

**Coupling of Peptide CRSWNKADNRSC (SEQ ID NO:5) to VEGF-$B_{167}$**

In addition to the amino and carboxyl group of the N- and C-terminus, this peptide has two functional sulfhydril groups and one -amino group of Lysine that can be used for the coupling to VEGF-$B_{167}$. If it is necessary to use the peptide in a cyclic structure, only the amino- and carboxyl groups are available. Because there are more reactive groups on the peptide, the amount of theoretical byproducts can increase.

Paragraph beginning at page 53, line 6, has been amended as follows:

**EXAMPLE 8**

**Carboxy-terminal (Ct) fusion of the targeting peptides ~~GGGVFNQ~~ GGGVFWQ (SEQ ID NO:1) and CRSWNKADNRSC (SEQ ID NO:5) to VEGF-$B_{167}$**

[Construction of plasmids pVEGF(BHG4S)$_3$,-GGGVFNQ and pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC and expression of the chimeric molecules in CHO cells]

Construction of plasmids pVEGF(B)-($G_4S$)$_3$,-GGGVFWQ and pVEGF(B)-($G_4S$)$_3$-CRSWNKADNRSC and expression of the chimeric molecules in CHO cells

The plasmids [pVEGF(B)-(G4S)$_3$-GGGVFNQ and pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC] pVEGF(B)-($G_4S$)$_3$-GGGVFWQ and pVEGF(B)-($G_4S$)$_3$-CRSWNKADNRSC contain the DNA sequences coding for the targeting peptides $NH_2$-GGGVFWQ-COOH (SEQ ID NO:1) and $NH_2$-CRSWNKADNRSC-COOH (SEQ ID NO:5), respectively, fused to the C-terminus of the VEGF-$B_{167}$ molecule via a [$NH_2$-(GGGGS) x3 – COOH] $NH_2$-($G_4S$)$_3$ –COOH (SEQ ID NO:8) hinge region. This type of linker is usually used to flexibly connect heavy and light chains in a single chain antibodies; alternatively, other connecting peptides, such as the natural hinge region present, in human immunoglobulin genes or oligo-proline or oligo-glycine linkers can be used. The linker peptide can, in addition, contain a protease cleavage site located between C-terminus of VEGF-$B_{167}$ and the linker (*e.g.*, a plasmin cleavage site) allowing, after high affinity targeting to normal or ischemic heart, the

release of a native VEGF-$B_{167}$ molecule. Due to the flexibility of the linker, the C-terminal fusion peptide does not interfere with receptor binding.

Paragraph beginning at page 53, line 23, has been amended as follows:

A series of modular plasmids are constructed to finally obtain plasmids [pVEGF(B)-(G4S)$_3$-GGGVFNQ and pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC] pVEGF(B)-($G_4$S)$_3$-GGGVFWQ and pVEGF(B)-($G_4$S)$_3$-CRSWNKADNRSC (*see* Materials and Methods, below). The intermediate plasmid pvegf-ss(l) provides the VEGF-B signal sequence followed by a HincII restriction site allowing for the convenient insertion of either the wild-type VEGF-$B_{167}$ sequence or any other desired N-terminal fusion peptide (*see* Example 'N-Terminal fusions'). The final constructs, the plasmids [pVEGF(B)-(G4S)3-GGGVFNQ and pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC] pVEGF(B)-($G_4$S)3-GGGVFWQ and pVEGF(B)-($G_4$S)$_3$-CRSWNKADNRSC, are transfected into CHO cells. Cotransfection with a selectable marker, selection of CHO cell clones and production of the proteins can be carried out using standard cell culture and biotechnology procedures (*see, e.g.*, Example 1). The purification of the chimeric proteins is performed according to standard protein chemistry procedures (chromatography using anion and/or cation exchange resins, gel filtration or affinity chromatography).

Paragraph beginning at page 54, line 5, has been amended as follows:

Construction of plasmids

**pSI-vegf-MCS(1)**

In a first step the commercially available vector pSI (Promega) is cut with BglII treated with Klenow Polymerase using standard conditions and religated. The resulting intermediate plasmid is designated pSI-B. Subsequently, pSI-B is digested with NheI and NotI and ligated with annealed [oligonucteotides] oligonucleotides P-vegfMCS(l) 5'-CTAGTACGTA TCTAGAGTCG ACACTAGTAG ATCTGATATC GCTAGCCTCG AGGCGGCGC CACGTGTACG TAGGCC-3' (SEQ ID NO:9), and P-vegfMCS(2) 5'-GGCCTACGTA CACGTGGCGG CCGCCTCGAG GCTAGCGATA TCAGATCTAC

TAGTGTCGAC TCTAGATACG TA-3' (SEQ ID NO:10). The resulting plasmid is sequenced employing the primer P-4371 (5'-AATACGACTCACTATAG-3' (SEQ ID NO:11)) and designated pS1-vegf-MCS(l). pvegf-ss(1). Insertion of a DNA stretch encoding the VEGF-$B_{167}$ signal sequence $Met^{1}$-$Ala^{21}$ including amino acid codons $Pro^{22}$, $Val^{23}$ and $Asp^{27}$ is done by ligating the Xbal/SalI cut vector pSI-vegf-MCS(1) with the annealed oligonucleotides P-ss(l) 5'-CTAG GCCACCATGAGCC CTCTGCTCCG CCGCCTGCTG CTCGCCGCAC TCCTGCAGCT GGCCCCCGCC CAGGCCCCTG -3' (SEQ ID NO:12) and P-ss(2) 5'-TCGACAGGGG CCTGGGCGGG GGCCAGCTGC AGGAGTGCGG CGAGCAGCAG GCGGCGGAGC AGAGGGCTCA TGGTGGC-3' (SEQ ID NO:13). The inserted region is sequenced (primer P-4371) and the resulting plasmid 15 named pvegf-ss(1). Amino acid codons $Val^{23}$ and $Asp^{27}$ form a HincII restriction site. This allows for the convenient insertion of either the wildtype VEGF-$B_{167}$ sequence (codons $Ser^{24}$ $Gln^{25}$ and $Pro^{26}$) or for any desired N-terminal fusion peptide.

Paragraph beginning at page 54, line 26, has been amended as follows:

**pvegf-d24/26**

In order to construct the vector pvegf-d24/26, VEGF-$B_{167}$ coding sequences corresponding to amino acid residues $Asp^{27}$ to $Arg^{188}$ are amplified as a 500bp PCR product in a standard PCR reaction employing primers 2-27/$_{167}$(1) 5'- GATCGTCGAC GCCCCTGGCC ACCAGAGGAA AGTGG -3' (SEQ ID NO:14) and P-27/$_{167}$(2) 5'-GATCAGATCT TCGCAGCTTC CGGCACCTGC AGGTG -3' (SEQ ID NO:15). The PCR product is digested with SalI/Bg1ll and the resulting 486bp fragment is cloned into SalI/BglII cut plasmid pvegf-ss(1).

Paragraph beginning at page 55, line 14, has been amended as follows:

**[PVEGF(B)-(G4S)$_3$] pVEGF(B)-($G_4S$)$_3$**

To complete the construction of the vector [pVEGF(B)-(G4S)$_3$] pVEGF(B)-($G_4S$)$_3$, annealed oligonucleotides P-Li(1) 5'- GATCTGGCGG CGGCGGCAGC GGCGGCGGCG GCAGCGGCGG CGGCGGCTCT G-3' (SEQ ID NO:16), and P-Li(2) 5'

CTAGCAGAGC CGCCGCCGCC GCTGCCGCCG CCGCCGCTGC CGCCGCCGCC A-3' (SEQ ID NO:17) encoding the [(Gly-Gly-Gly-Gly-Ser) x3] $(G_4S)_3$ (SEQ ID NO:8) linker sequence, are inserted into Bg1II/NheI cut vector pVEGF(B)-F.

Paragraph beginning at page 55, line 21, has been amended as follows:

**[PVEGF(B)G4S)$_3$-GGGVFNQ] pVEGF(B)$(G_4S)_3$-GGGVFWQ**

Construction of [pVEGF(B)-(G4S)$_3$-GGGVFNQ] pVEGF(B)-$(G_4S)_3$-GGGVFWQ is done by ligation of NheI/NotI cut vector pVEGF(B)-$(G_4S)_3$, with annealed oligonucleotides P-D(1) 5'- CTAGC GGC GGG GGC GTG TTC TGG CAG TAAGC-3' (SEQ ID NO:18), and P-D(2) 5'- GGCCGCTT ACTGCCAGAA CACGCCCCCG CCG-3' (SEQ ID NO:19). The plasmid [pVEGF(B)-(G4S)$_3$,-GGGVFNQ] pVEGF(B)-$(G_4S)_3$-GGGVFWQ contains the DNA sequences coding for the targeting peptide [$NH_2$-GGGVPWQ-COOH] $NH_2$-GGGVFWQ-COOH (SEQ ID NO:1) fused to the C-terminus of the VEGF-$B_{167}$ cDNA via a [$NH_2$-(GGGGS) x3 –COOH] $NH_2$-$(G_4S)_3$–COOH (SEQ ID NO:8) hinge region.

Paragraph beginning at page 55, line 29, has been amended as follows:

**[pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC] pVEGF(B)-$(G_4S)_3$-CRSWNKADNRSC**

Construction of [pVEGF(B)-(G4S)$_3$-CRSWNKADNRSC] pVEGF(B)-$(G_4S)_3$-CRSWNKADNRSC was done by ligation of NheI/NotI cut vector [pVEGF(B)-(G4S)] pVEGF(B)-$(G_4S)_3$, with annealed oligonucleotides P-CRSWNKADNRSC(1) 5'-CTAGCTGCC GCAGCTGGAA CAAAGCCGAC AACCGCAGCT GCTAAGC-3' (SEQ ID NO:20) and P-CRSWNKADNRSC(2) 5'-GGCCGCTT AGCAGCTGCG [GTTGTCGGCT] GTTGTCGGCT-3' (SEQ ID NO:21).

Paragraph beginning at page 56, line 4, has been amended as follows:

## EXAMPLE 9

**Amino-terminal (Nt) fusion of the targeting peptide CRSWNKADNRSC (SEQ ID NO:5) to VEGF-$B_{186}$**

Construction of the plasmid pVEGF(B)-Nt-CRSWNKADNRSC and expression of the chimeric molecules in CHO cells

The plasmid pVEGF(B)-Nt-CRSWNKADNRSC contains the DNA sequences coding for the heart tissue target peptide $NH_2$-CRSWNKADNRSC-COOH (SEQ ID NO:5) inserted between the signal peptide and the N-terminus of the VEGF-$B_{186}$ molecule via a [$NH_2$-(GGGGS) x3-COOH] $NH_2$-$(G_4S)_3$-COOH (SEQ ID NO:8) hinge region. Other linker peptides containing functional elements may be used (*see* Example 8 above). The N-terminal fusion allows the natural proteolytic processing occurring with the VEGF-$B_{186}$ molecule without loss of the targeting molecule. Since the N-terminus appears to be located distal to the membrane binding face of the dimeric VEGF molecule, the fused targeting peptide can interact without steric hindrance with its receptor. Part of the series of modular plasmids described in example 8 is used to further construct the plasmid pVEGF(B)-Nt- CRSWNKADNRSC (*see* Materials and Methods). The final construct is transfected into CHO cells. Cotransfection with a selection marker, selection of CHO cell clones and production of protein is carried out using standard cell culture and biotechnology procedures (*see* Example 1). The purification of the chimeric proteins is done according to standard protein chemistry procedures.

Paragraph beginning at page 56, line 24, has been amended as follows:

Materials and Methods

Construction of plasmids

**pVEGF(B)186-d24/26**

Construction of pVEGF(B)186-d24/26 is done by digestion of pvegf-d24/26-dH (*see* Example 8) with SalI and BglII. A 492bp fragment is removed by gel purification. This step deletes DNA sequences coding for amino acids Asp27 to Arg188 of VEGF(B)167 from plasmid pvegf-d24/26-dH (*see* Example 8). Subsequently a 553 bp

This application is a divisional of, and claims the benefit of priority from, U.S. Patent Application Serial No. 09/327,045, filed June 7, 1999, abandoned, the full disclosure of which is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 27, line 2, with the following rewritten paragraph:

Preferred targeting molecules of the invention comprise an amino acid sequence selected from the group comprising GGGVFWQ, HGRVRPH, VVLVTSS, CLHRGNSC, and CRSWNKADNRSC (SEQ ID NO:1-5, respectively) using the *in vivo* panning procedure described above and referenced below. The GGGVFWQ , HGRVRPH, VVLVTSS, and CLHRGNSC (SEQ ID NO:1-4, respectively) peptides selectively bind to normal cardiac endothelium. More specifically, the GGGVFWQ (SEQ ID NO:1) peptide showed a 5-fold enrichment to normal cardiac vasculature, while the HGRVRPH, VVLVTSS, CLHRGNSC (SEQ ID NO:2-4, respectively) peptides showed a 2-fold enrichment to normal cardiac vasculature. The CRSWNKADNRSC (SEQ ID NO:5) peptide showed 5-fold enrichment to ischemic myocardium. Details of how these peptides were identified and their properties are described in U.S.S.N. 09/326,718 [Campbell & Flores LLP Attorney Docket # P-LJ 3512] filed on even date herewith which is specifically incorporated herein by reference.

Please replace the paragraph beginning at page 48, line 25, with the following rewritten paragraph:

The plasmid pVEGF-Bwt167 is constructed by insertion of a 580bp PCR product derived from phage Lambda gt11-VEGF-Bwt167 into the expression plasmid pSI (Promega, Inc.). This phage is obtainable by screening a human fibrosarcoma cDNA library in lambda g11 (obtainable from Clontech, Inc.). The PCR reaction is performed employing the Advantage KlenTaq Polymerase Mix system (Clontech. Inc.) in a final volume of 100 microliter containing lng of the plasmid template, 0.5μM of primers P-wt167(l) 5'-GATCGCTAGC GGCAGCATGA GCCCTCTGCT CCGCCGCCTG-3' (SEQ ID NO:6) and P-wt167(2) 5'-TGACGCGGCC GCTCACCTTC GCAGCTTCCG GCACCTGCAG-3' (SEQ ID NO:7) as well as 0.2mM dNTPs, using the conditions 93°C 30 sec, 55°C 30 sec, 72°C 30

SalI/BglII cut PCR product coding for amino acid $Asp^{27}$-$Ala^{207}$ of VEGF(B)186 is inserted. PCR is done as a standard PCR reaction employing primers P-27/167(1) and P-27/186(1) (5'-TGACAGATCT CTAAGCCCCG CCCTTGGCAA CGGAGG-3') (SEQ ID NO:22) and VEGF(B)186 cDNA as a template. In the final plasmid pVEGF(B)186-d24/26 amino acids $Asp^{27}$ to $Arg^{188}$ of VEGF(B)167 are replaced by amino acids $Asp^{27}$ to $Ala^{207}$ of VEGF(B)186, amino acids $Met^{1}$ to $Val^{23}$ are common to both VEGF(B) forms whereas amino acids $Ser^{24}$, $Gln^{25}$ and $Pro^{26}$ are still missing.

Paragraph beginning at page 57, line 7, has been amended as follows:

**pVEGF(B)186-Nt-R13**

Construction of pVEGF(B)186-Nt-CRSWNKADNRSC is done by ligating HindII cleaved vector pVEGF(B)186-d24/26 with annealed oligonucleotides P-Nt-CRSWNKADNRSC(1) 5'- TGCCGCAGCT GGAACAAAGC CGACAACCGC AGCTGCTCCC AGCCT-3' (SEQ ID NO:23) and P-Nt-CRSWNKADNRSC(2) 5'-AGGCTGGGAG CAGCTGCGGT TGTCGGCTTT GTTCCAGCTG CGGCA-3' (SEQ ID NO:24). The plasmid containing the oligonucleotides inserted into the opposite direction is also isolated and designated pVEGF(B)186-Nt-antisense.